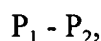


WE CLAIM:

1. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

2. The method of Claim 1 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

3. The method of Claim 1 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

4. The method of Claim 1 wherein Xaa₃ is lysine.

5. The method of Claim 1 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

6. The method of Claim 5 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

7. The method of Claim 6 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

8. The method of Claim 7 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

9. The method of Claim 1 wherein n is 0-10.

10. The method of Claims 9 wherein n is 0-5.

11. The method of Claim 10 wherein n is 0.

12. The method of Claim 1 wherein P₂ comprises a metal-binding sequence.

13. The method of Claim 12 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

14. The method of Claim 13 wherein Xaa₅ is Orn or Lys.

15. The method of Claim 1 wherein at least one of the amino acids of P₁ other than β -alanine is a D-amino acid.

16. The method of Claim 15 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids..

17 The method of Claim 16 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

18. The method of Claim 15 wherein at least 50% of the amino acids of P₂ are D-amino acids.

19. The method of Claim 16 wherein at least 50% of the amino acids of P₂ are D-amino acids.

20. The method of Claim 17 wherein at least 50% of the amino acids of P₂ are D-amino acids.

21. The method of any one of Claims 1-20 wherein the animal is in need of the peptide because of the need to reperfuse an ischemic tissue or organ of the animal.

22. The method of Claim 21 wherein the animal is suffering from cerebrovascular ischemia and the ischemic tissue is located in the brain of the animal.

23. The method of Claim 21 wherein the animal is suffering from cardiovascular ischemia and the ischemic tissue is located in the heart of the animal.

24. The method of Claim 21 wherein the peptide is administered prior to reperfusion, simultaneously with reperfusion, after reperfusion, or combinations thereof.

25. The method of any one of Claims 1-20 wherein the animal is in need of the peptide because of neurological trauma.

26. The method of any one of Claims 1-20 wherein the animal is in need of the peptide because it is suffering from a neurodegenerative disease.

27. The method of any one of Claims 1-20 wherein the peptide is administered prophylactically.

28. The method of Claim 27 wherein the peptide is administered to an animal exhibiting symptoms of possible cerebrovascular ischemia or possible cardiovascular ischemia while the animal is being diagnosed.

29. The method of Claim 27 wherein the peptide is administered to an animal prior to surgery, during surgery, after surgery, or combinations thereof.

30. The method of Claim 29 wherein the surgery is open-heart surgery or surgery to transplant an organ into the animal.

31. The method of Claim 27 wherein the peptide is administered to an animal prior to radiation therapy, during radiation therapy, after radiation therapy, or combinations thereof.

a 32. The method of any one of Claims 1-20 wherein at least one amino acid of P₁ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

33. The method of Claim 32 wherein the animal is in need of the peptide because of the need to reperfuse an ischemic tissue or organ of the animal.

34. The method of Claim 33 wherein the animal is suffering from cerebrovascular ischemia and the ischemic tissue is located in the brain of the animal.

35. The method of Claim 33 wherein the animal is suffering from cardiovascular ischemia and the ischemic tissue is located in the heart of the animal.

36. The method of Claim 33 wherein the peptide is administered prior to reperfusion, simultaneously with reperfusion, after reperfusion, or combinations thereof.

37. The method of Claim 32 wherein the animal is in need of the peptide because of neurological trauma.

38. The method of Claim 32 wherein the animal is in need of the peptide because it is suffering from a neurodegenerative disease.

39. The method of Claim 32 wherein the peptide is administered prophylactically.

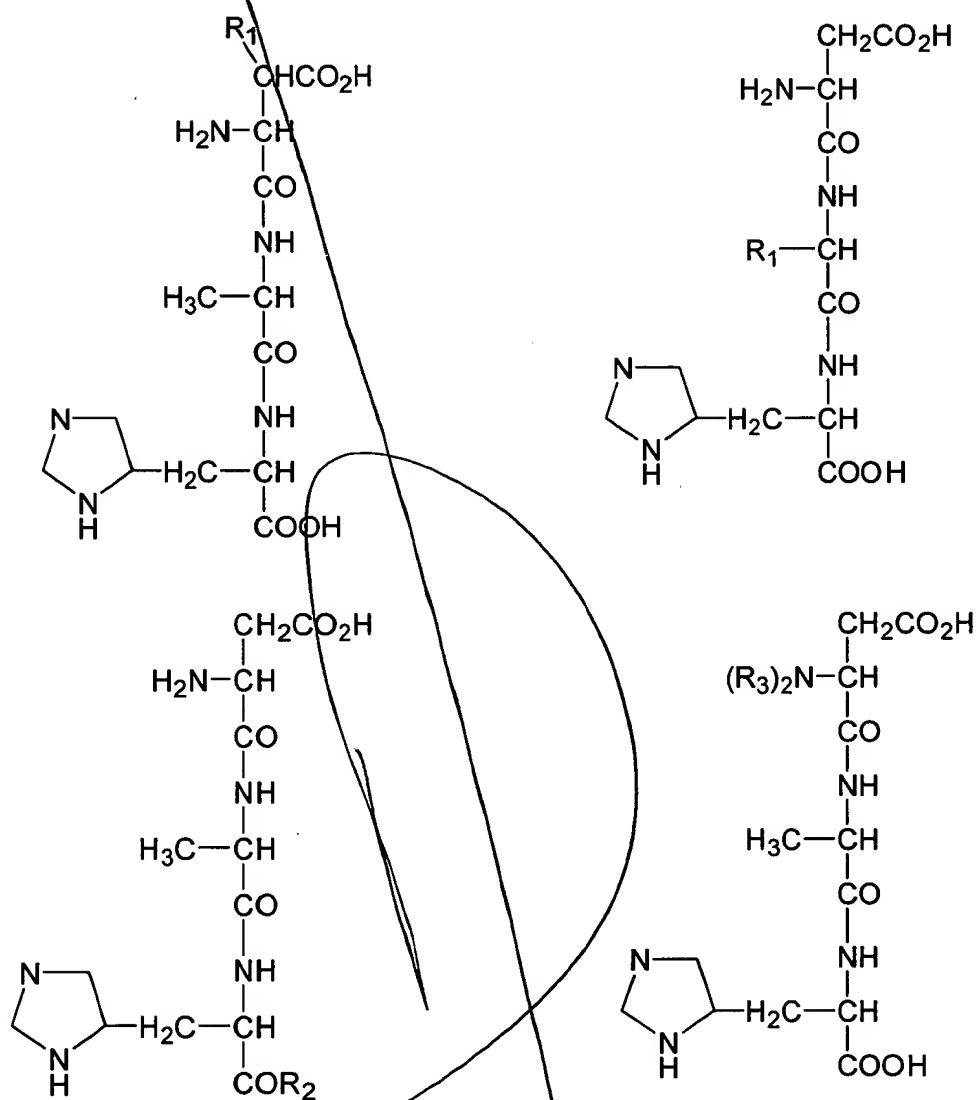
40. The method of Claim 39 wherein the peptide is administered to an animal exhibiting symptoms of possible cerebrovascular ischemia or possible cardiovascular ischemia while the animal is being diagnosed.

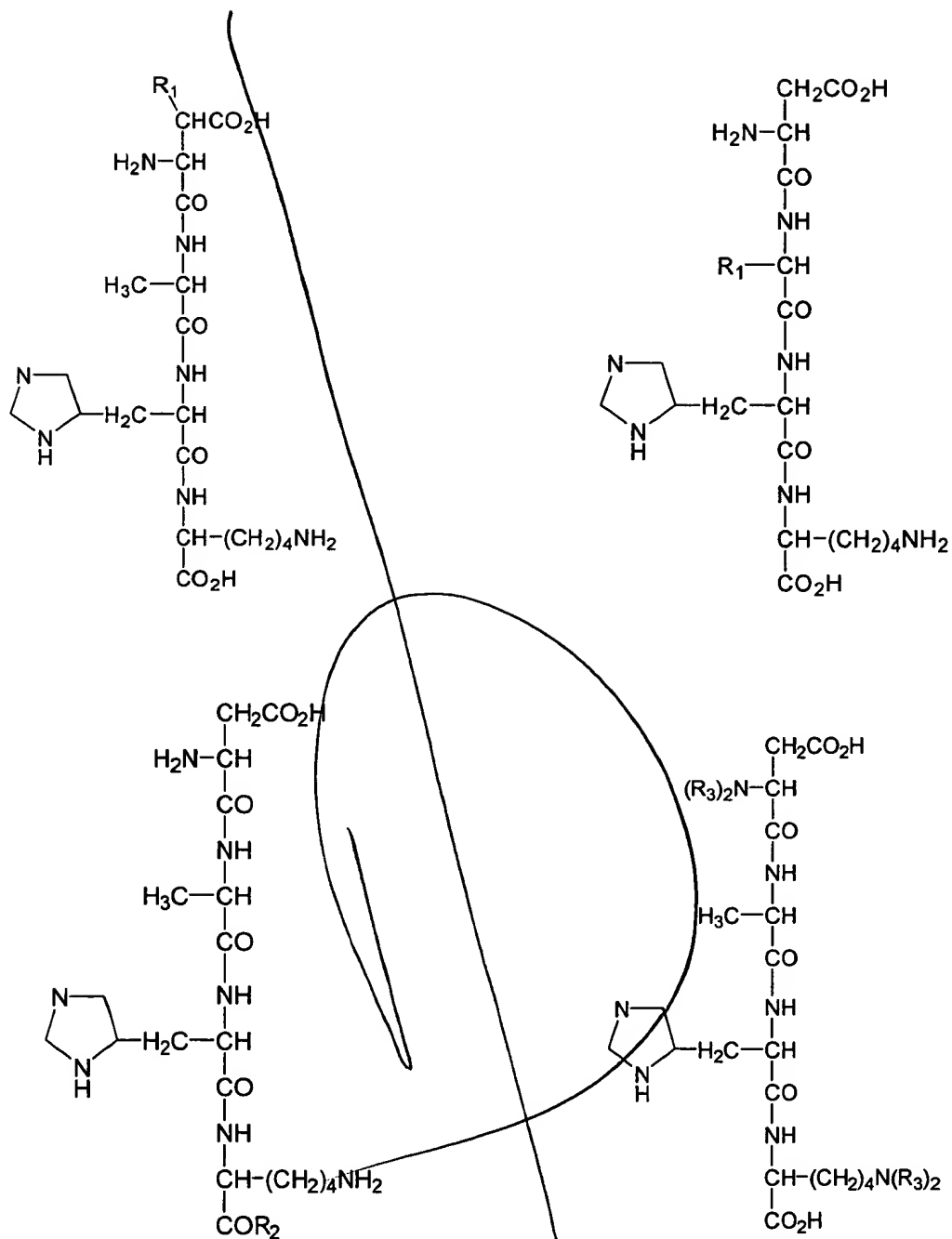
41. The method of Claim 39 wherein the peptide is administered to an animal prior to surgery, during surgery, after surgery, or combinations thereof.

42. The method of Claim 41 wherein the surgery is open-heart surgery or surgery to transplant an organ into the animal.

43. The method of Claim 39 wherein the peptide is administered to an animal prior to radiation therapy, during radiation therapy, after radiation therapy, or combinations thereof.

44. The method of Claim 32 wherein P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R₃ is H, a non-peptide, metal-binding functional group or the two R₃ groups together form a non-peptide, metal-binding functional group.

45. The method of Claim 44 wherein the animal is in need of the peptide because of the need to reperfuse an ischemic tissue or organ of the animal.

46. The method of Claim 45 wherein the animal is suffering from cerebrovascular ischemia and the ischemic tissue is located in the brain of the animal.

47. The method of Claim 45 wherein the animal is suffering from cardiovascular ischemia and the ischemic tissue is located in the heart of the animal.

48. The method of Claim 45 wherein the peptide is administered prior to reperfusion, simultaneously with reperfusion, after reperfusion, or combinations thereof.

49. The method of Claim 44 wherein the animal is in need of the peptide because of neurological trauma.

50. The method of Claim 44 wherein the animal is in need of the peptide because it is suffering from a neurodegenerative disease.

51. The method of Claim 44 wherein the peptide is administered prophylactically.

52. The method of Claim 51 wherein the peptide is administered to an animal exhibiting symptoms of possible cerebrovascular ischemia or possible cardiovascular ischemia while the animal is being diagnosed.

53. The method of Claim 51 wherein the peptide is administered to an animal prior to surgery, during surgery, after surgery, or combinations thereof.

54. The method of Claim 53 wherein the surgery is open-heart surgery or surgery to transplant an organ into the animal.

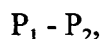
55. The method of Claim 51 wherein the peptide is administered to an animal prior to radiation therapy, during radiation therapy, after radiation therapy, or combinations thereof.

a 56. The method of any one of Claims 1-20 wherein at least one amino acid of P₂ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a

non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

57. The method of Claim 32 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions

58. A method of reducing the damage done by reactive oxygen species (ROS) in a tissue or an organ that has been removed from an animal comprising contacting the tissue or organ with a solution containing an effective amount of a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or
Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

59. The method of Claim 58 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

60. The method of Claim 58 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

61. The method of Claim 58 wherein Xaa₃ is lysine.

62. The method of Claim 58 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

63. The method of Claim 62 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

64. The method of Claim 63 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

65. The method of Claim 64 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

66. The method of Claim 58 wherein n is 0-10.

67. The method of Claim 66 wherein n is 0-5.

68. The method of Claim 67 wherein n is 0.

69. The method of Claim 58 wherein P₂ comprises a metal-binding sequence.

70. The method of Claim 69 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

71. The method of Claim 70 wherein Xaa₅ is Orn or Lys.

72. The method of Claim 58 wherein at least one of the amino acids of P₁ other than β -alanine is a D-amino acid.

73. The method of Claim 72 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids..

74. The method of Claim 73 wherein all of the amino acids of P_1 other than β -alanine are D-amino acids.

75. The method of Claim 72 wherein at least 50% of the amino acids of P_2 are D-amino acids.

76. The method of Claim 73 wherein at least 50% of the amino acids of P_2 are D-amino acids.

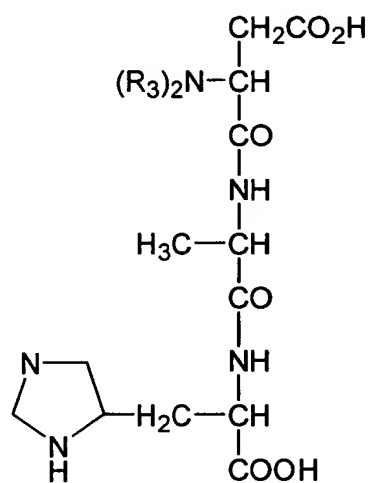
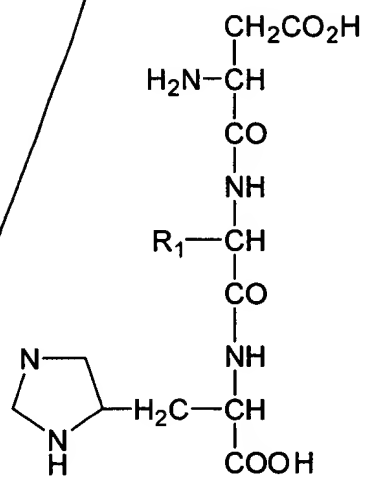
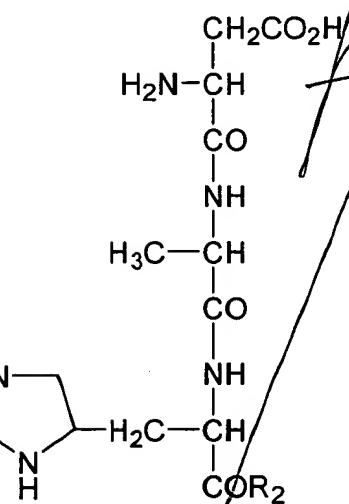
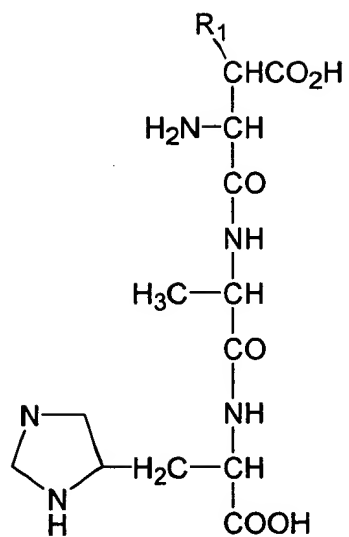
77. The method of Claim 74 wherein at least 50% of the amino acids of P_2 are D-amino acids.

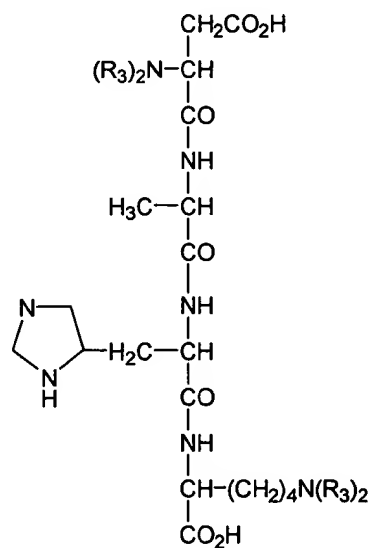
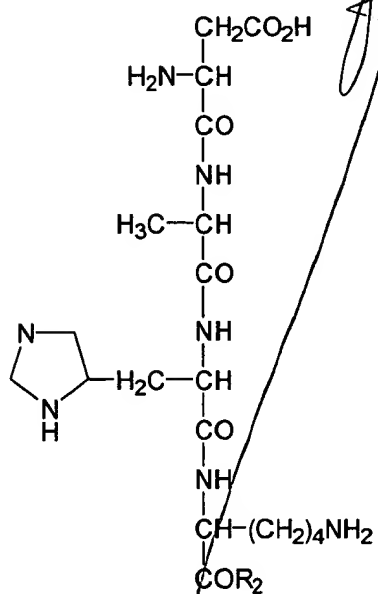
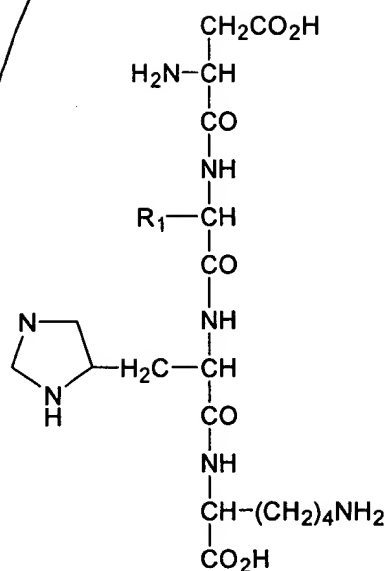
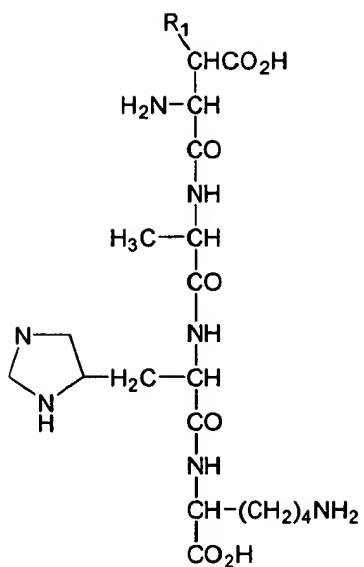
78. The method of any one of Claims 58-77 wherein the tissue or organ is transplanted into an animal after being contacted with the solution containing the peptide.

79. The method of any one of Claims 58-77 wherein at least one amino acid of P_1 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

80. The method of Claim 79 wherein the tissue or organ is transplanted into an animal after being contacted with the solution containing the peptide.

81. The method of Claim 79 wherein P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

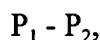
R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

82. The method of Claim 81 wherein the tissue or organ is transplanted into an animal after being contacted with the solution containing the peptide.

83. The method of any one of Claims 58-77 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

84. The method of Claim 79 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

85. A method of reducing the concentration of a metal in an animal in need thereof comprising administering to the animal an effective amount of a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His; or
Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

86. The method of Claim 85 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

87. The method of Claim 85 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

88. The method of Claim 85 wherein Xaa₃ is lysine.

89. The method of Claim 85 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

90. The method of Claim 89 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

91. The method of Claim 90 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

92. The method of Claim 91 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

93. The method of Claim 85 wherein n is 0-10.

94. The method of Claim 85 wherein P₂ comprises a metal-binding sequence.

95. The method of Claim 94 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

96. The method of Claim 95 wherein Xaa₅ is Orn or Lys.

97. The method of Claim 85 wherein at least one of the amino acids of P₁ other than β-alanine is a D-amino acid.

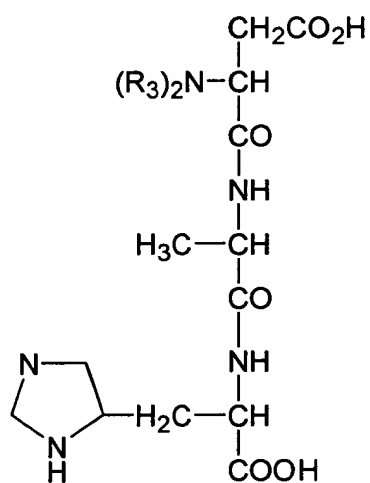
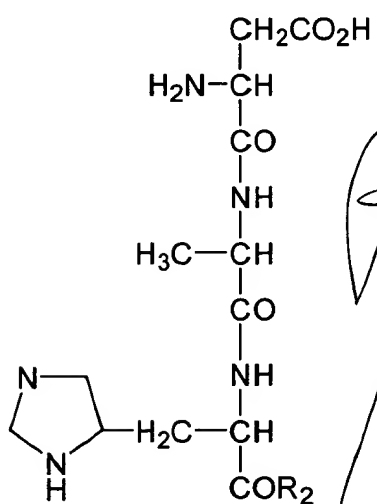
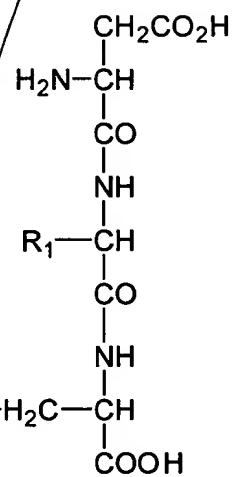
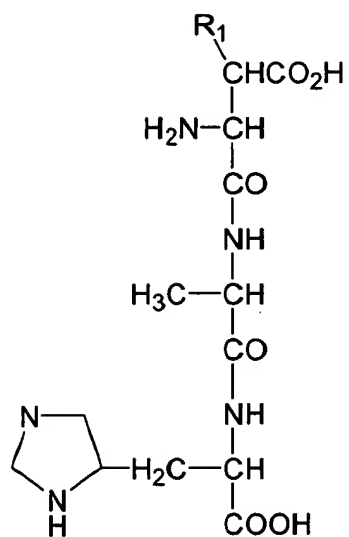
98. The method of Claim 97 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids..

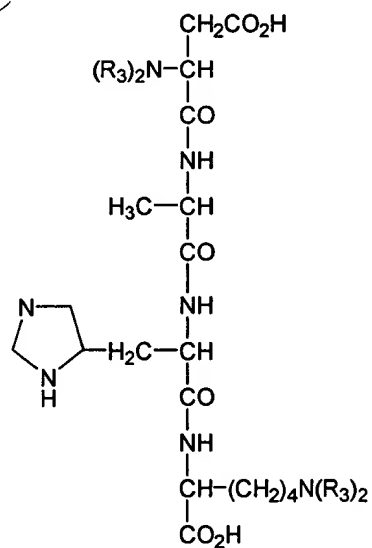
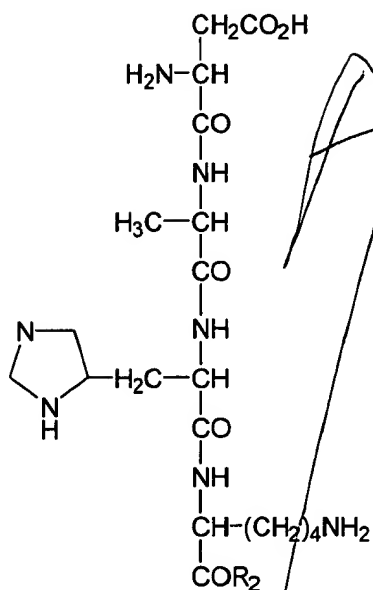
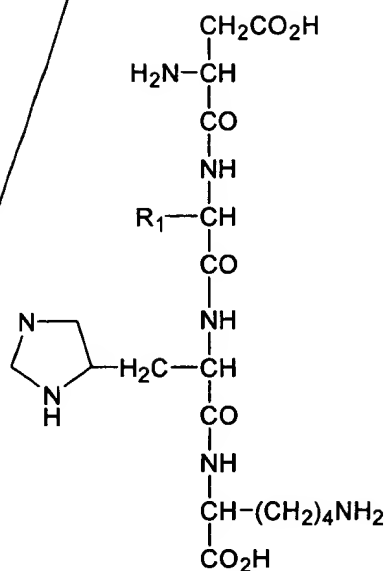
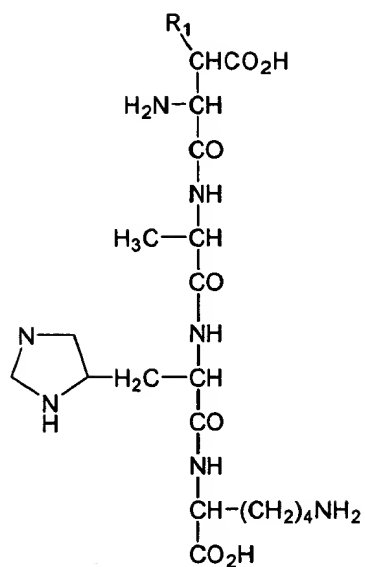
99. The method of Claim 98 wherein all of the amino acids of P₁ other than β-alanine are D-amino acids.

100. The method of Claim 97 wherein at least 50% of the amino acids of P₂ are D-amino acids.

101. The method of any one of Claims 85-100 wherein at least one amino acid of P₁ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

102. The method of Claim 101 wherein P₁ has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

103. The method of any one of Claims 85-100 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

104. The method of Claim 101 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

105. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

106. The method of Claim 105 wherein the peptide contains from 2-10 amino acids.

107. The method of Claim 106 wherein the peptide contains from 3-5 amino acids.

108. The method of Claim 105, 106, or 107 wherein the amino acids of the peptide are D-amino acids.

109. A method of reducing the damage done by reactive oxygen species (ROS) in a tissue or an organ that has been removed from an animal comprising contacting the tissue or organ with a solution containing an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

110. The method of Claim 109 wherein the peptide contains from 2-10 amino acids.

111. The method of Claim 110 wherein the peptide contains from 3-5 amino acids.

112. The method of Claim 109, 110, or 111 wherein the amino acids of the peptide are D-amino acids.

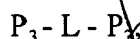
113. A method of reducing the concentration of metal in an animal in need thereof comprising administering to the animal an effective amount of a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

114. The method of Claim 113 wherein the peptide contains from 2-10 amino acids.

115. The method of Claim 114 wherein the peptide contains from 3-5 amino acids.

116. The method of Claim 113, 114, or 115 wherein the amino acids of the peptide are D-amino acids.

117. A method of reducing the damage done by reactive oxygen species (ROS) in an animal comprising administering to the animal an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

118. The method of Claim 117 wherein each P_3 contains 2-10 amino acids.

119. The method of Claim 117 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His; or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

120. The method of Claim 119 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

121. The method of Claim 119 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

122. The method of Claim 119 wherein Xaa₃ is lysine.

123. The method of Claim 119 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

124. The method of Claim 123 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

125. The method of Claim 124 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

126. The method of Claim 125 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

127. The method of Claim 119 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

128. The method of Claim 127 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

129. The method of Claim 119 wherein both P₃ peptides are P₁.

130. The method of Claims 117 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

131. The method of Claim 117 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

132. The method of Claim 117 wherein L is neutral.

133. The method of Claim 117 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

134. The method of Claim 133 wherein L contains 2-8 carbon atoms.

135. The method of Claim 117 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

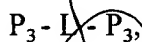
136. The method of Claim 135 wherein L contains 3-5 carbon atoms.

137. The method of Claim 117 wherein L is a nitrogen-containing heterocyclic alkane residue.

138. The method of Claim 137 wherein L is a piperazide.

139. The method of Claim 117 wherein L is a glyceryl ester.

140. A method of reducing the damage done by reactive oxygen species (ROS) in a tissue or an organ that has been removed from an animal comprising contacting the tissue or organ with a solution containing an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

141. The method of Claim 140 wherein each P_3 contains 2-10 amino acids.

142. The method of Claim 140 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His; or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

143. The method of Claim 142 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

144. The method of Claim 142 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

145. The method of Claim 142 wherein Xaa₃ is lysine.

146. The method of Claim 142 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

147. The method of Claim 146 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

148. The method of Claim 147 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

149. The method of Claim 148 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

150. The method of Claim 142 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

151. The method of Claim 150 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

152. The method of Claim 142 wherein both P₃ peptides are P₁.

153. The method of Claims 140 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

154. The method of Claim 140 wherein P_3 comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P_3 .

155. The method of Claim 140 wherein L is neutral.

156. The method of Claim 140 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

157. The method of Claim 156 wherein L contains 2-8 carbon atoms.

158. The method of Claim 140 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

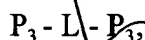
159. The method of Claim 158 wherein L contains 3-5 carbon atoms.

160. The method of Claim 140 wherein L is a nitrogen-containing heterocyclic alkane residue.

161. The method of Claim 160 wherein L is a piperazine.

162. The method of Claim 140 wherein L is a glyceryl ester.

163. A method of reducing the concentration of a metal in an animal in need thereof comprising administering to the animal an effective amount of a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

164. The method of Claim 163 wherein each P_3 contains 2-10 amino acids.

165. The method of Claim 163 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

166. The method of Claim 165 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

167. The method of Claim 165 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

168. The method of Claim 165 wherein Xaa₃ is lysine.

169. The method of Claim 165 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

170. The method of Claim 169 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

171. The method of Claim 170 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

172. The method of Claim 171 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

173. The method of Claim 165 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

174. The method of Claim 173 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

175. The method of Claim 165 wherein both P₃ peptides are P₁.

176. The method of Claims 163 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability

of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

177. The method of Claim 163 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

178. The method of Claim 163 wherein L is neutral.

179. The method of Claim 163 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

180. The method of Claim 179 wherein L contains 2-8 carbon atoms.

181. The method of Claim 163 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

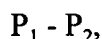
182. The method of Claim 181 wherein L contains 3-5 carbon atoms.

183. The method of Claim 163 wherein L is a nitrogen-containing heterocyclic alkane residue.

184. The method of Claim 183 wherein L is a piperazide.

185. The method of Claim 163 wherein L is a glyceryl ester.

186. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a peptide having the formula:



wherein:

P₁ is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P₂ is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

187. The composition of Claim 186 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

188. The composition of Claim 186 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

189. The composition of Claim 186 wherein Xaa₃ is lysine.

190. The composition of Claim 186 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

191. The composition of Claim 190 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

192. The composition of Claim 191 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

193. The composition of Claim 192 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

194. The composition of Claim 186 wherein n is 0-10.

195. The composition of Claims 194 wherein n is 0-5.

196. The composition of Claim 195 wherein n is 0.

197. The composition of Claim 186 wherein P₂ comprises a metal-binding sequence.

198. The composition of Claim 197 wherein P₂ comprises one of the following sequences:

$(Xaa_4)_m$ Xaa₃ His Xaa₂ Xaa₅,
 $(Xaa_4)_m$ His Xaa₂ Xaa₅,
 $(Xaa_4)_m$ Xaa₅ Xaa₂ His Xaa₃, or
 $(Xaa_4)_m$ Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

199. The composition of Claim 198 wherein Xaa₅ is Orn or Lys.

200. The composition of Claim 186 wherein at least one of the amino acids of P₁ other than β-alanine is a D-amino acid.

201. The composition of Claim 200 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids..

202. The composition of Claim 201 wherein all of the amino acids of P₁ other than β-alanine are D-amino acids.

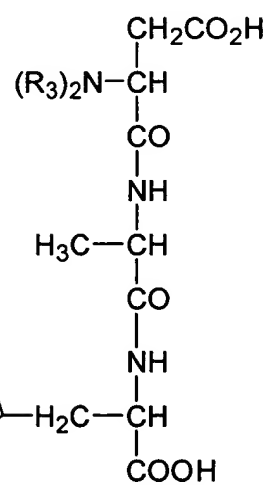
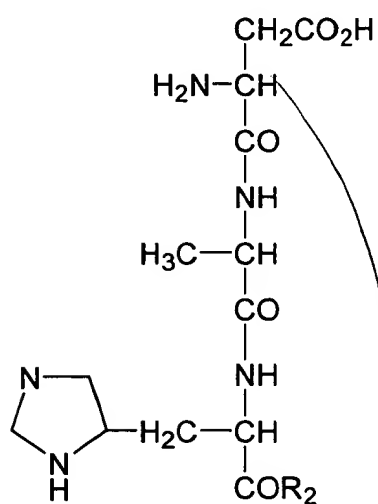
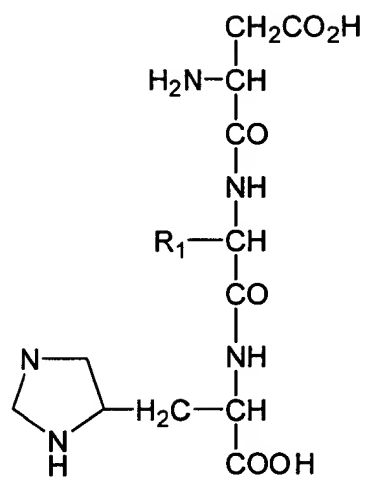
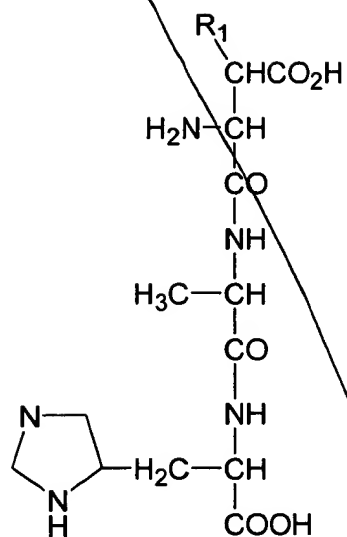
203. The composition of Claim 200 wherein at least 50% of the amino acids of P₂ are D-amino acids.

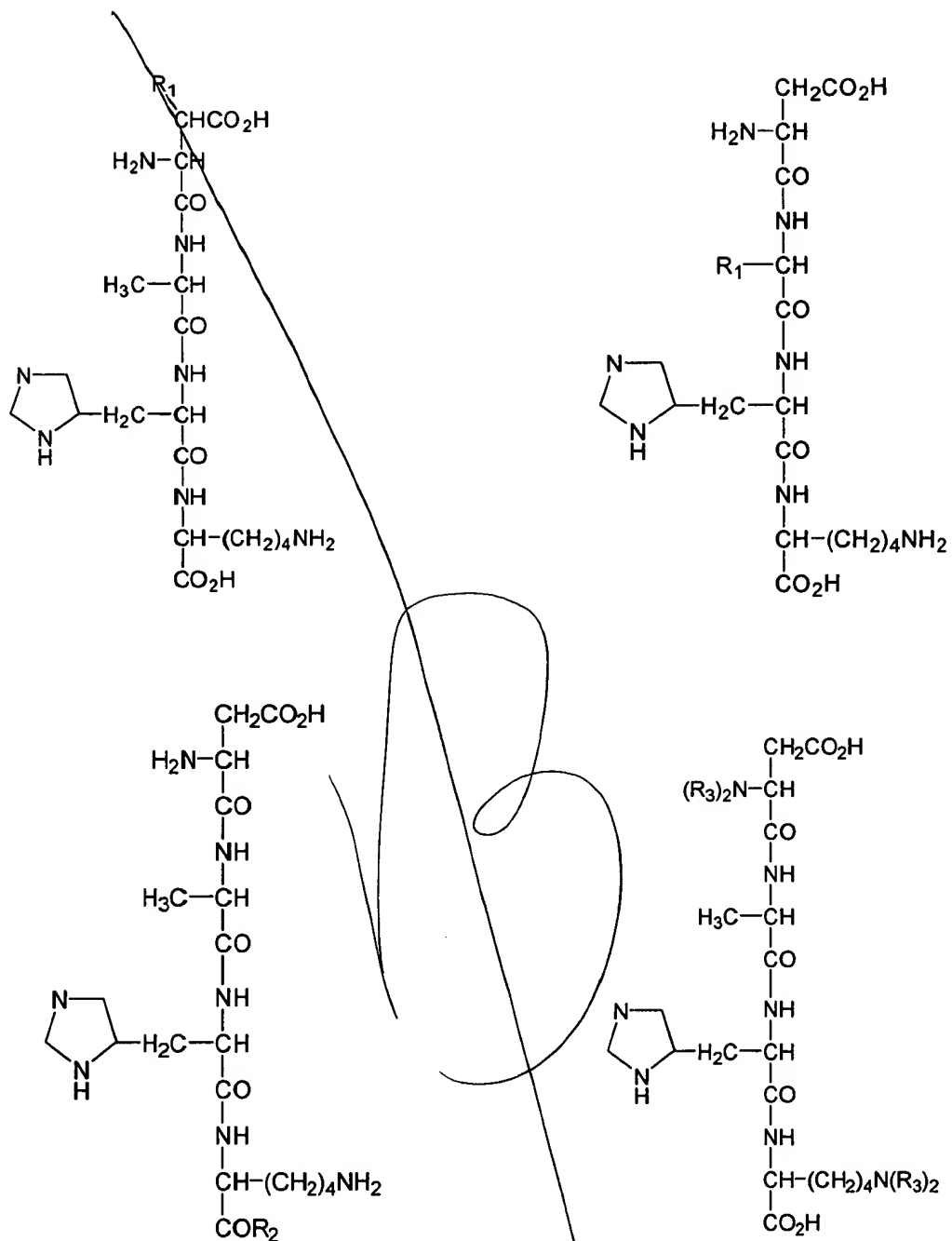
204. The composition of Claim 201 wherein at least 50% of the amino acids of P₂ are D-amino acids.

205. The composition of Claim 202 wherein at least 50% of the amino acids of P₂ are D-amino acids.

206. The composition of any one of Claims 186-205 wherein at least one amino acid of P₁ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

207. The composition of Claim 206 wherein P₁ has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

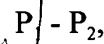
R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

a 208. The composition of any one of Claims 186-205 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

209. The composition of Claim 207 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions

210. A kit comprising a container holding a peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or
Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid; and

n is 0-100;

or a physiologically-acceptable salt thereof.

211. The kit of Claim 210 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

212. The kit of Claim 210 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

213. The kit of Claim 210 wherein Xaa₄ is lysine.

214. The kit of Claim 210 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

215. The kit of Claim 214 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

216. The kit of Claim 215 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

217. The kit of Claim 216 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

218. The kit of Claim 210 wherein n is 0-10.

219. The kit of Claims 218 wherein n is 0-5.

220. The kit of Claim 219 wherein n is 0.

221. The kit of Claim 210 wherein P₂ comprises a metal-binding sequence.

222. The kit of Claim 221 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

223. The kit of Claim 222 wherein Xaa₅ is Orn or Lys.

224. The kit of Claim 210 wherein at least one of the amino acids of P_1 other than β -alanine is a D-amino acid.

225. The kit of Claim 224 wherein Xaa_1 is a D-amino acid, His is a D-amino acid, or both Xaa_1 and His are D-amino acids..

226 The kit of Claim 225 wherein all of the amino acids of P_1 other than β -alanine are D-amino acids.

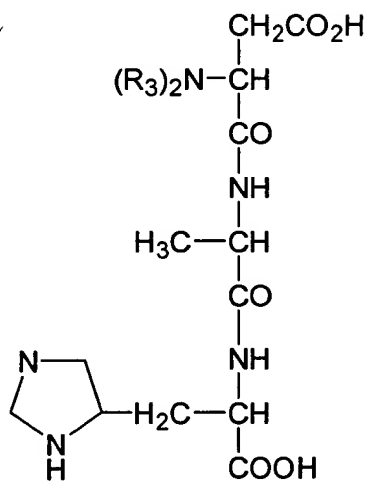
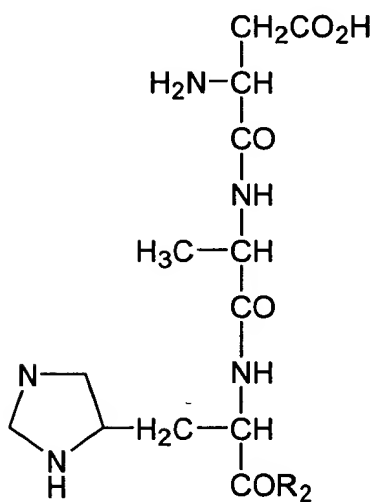
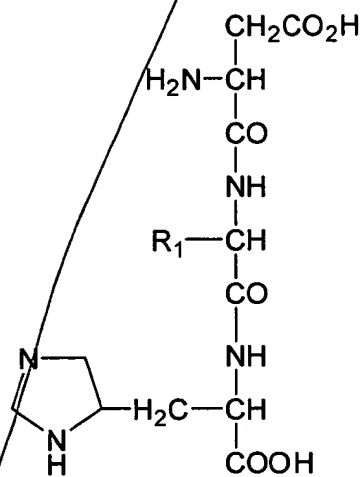
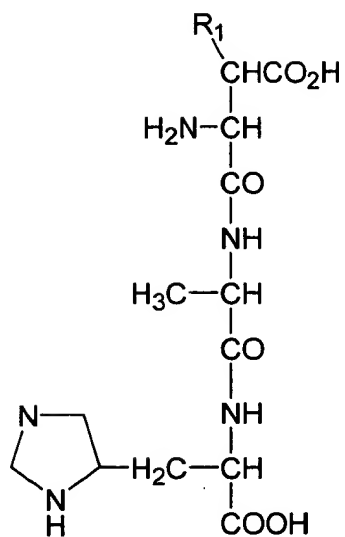
227. The kit of Claim 224 wherein at least 50% of the amino acids of P_2 are D-amino acids.

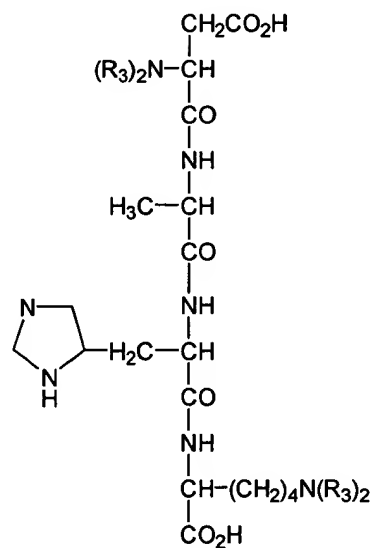
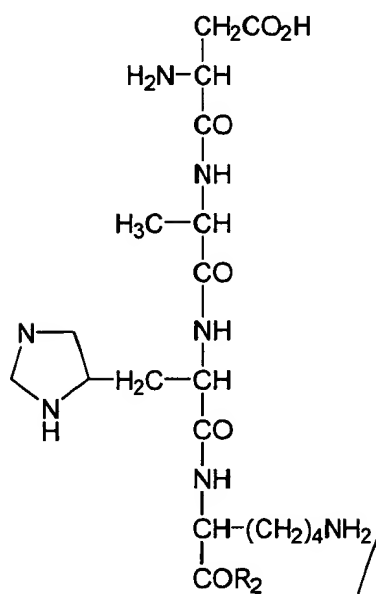
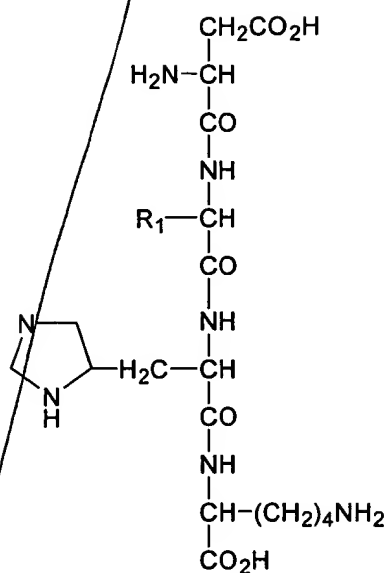
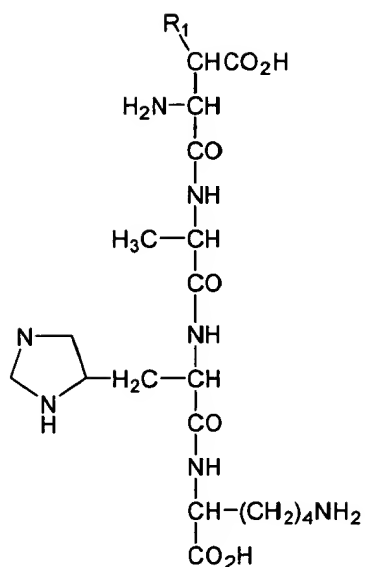
228. The kit of Claim 225 wherein at least 50% of the amino acids of P_2 are D-amino acids.

229. The kit of Claim 226 wherein at least 50% of the amino acids of P_2 are D-amino acids.

230. The kit of any one of Claims 210-229 wherein at least one amino acid of P_1 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

231. The kit of Claim 230 wherein P_1 has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

232. The kit of any one of Claims 210-229 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

233. The kit of Claim 231 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions

234. A pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

235. The composition of Claim 234 wherein the peptide contains from 2-10 amino acids.

236. The composition of Claim 235 wherein the peptide contains from 3-5 amino acids.

237. The composition of Claim 234, 235, or 236 wherein the amino acids of the peptide are D-amino acids.

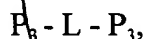
238. A kit comprising a container holding a metal-binding peptide having attached thereto a non-peptide, metal-binding functional group.

239. The kit of Claim 238 wherein the peptide contains from 2-10 amino acids.

240. The kit of Claim 239 wherein the peptide contains from 3-5 amino acids.

241. The kit of Claim 238, 239 or 240 wherein the amino acids of the peptide are D-amino acids.

242. A composition comprising a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

243. The composition of Claim 242 wherein each P_3 contains 2-10 amino acids.

244. The composition of Claim 242 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

245. The composition of Claim 244 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

246. The composition of Claim 244 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

247. The composition of Claim 244 wherein Xaa₃ is lysine.

248. The composition of Claim 244 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

249. The composition of Claim 248 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

250. The composition of Claim 249 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

251. The composition of Claim 250 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

252. The composition of Claim 244 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

253. The composition of Claim 252 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

254. The composition of Claim 244 wherein both P₃ peptides are P₁.

255. The composition of Claims 242 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

256. The composition of Claim 242 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

257. The composition of Claim 242 wherein L is neutral.

258. The composition of Claim 244 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

259. The composition of Claim 258 wherein L contains 2-8 carbon atoms.

260. The composition of Claim 244 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

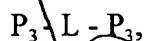
261. The composition of Claim 260 wherein L contains 3-5 carbon atoms.

262. The composition of Claim 244 wherein L is a nitrogen-containing heterocyclic alkane residue.

263. The composition of Claim 262 wherein L is a piperazide.

264. The composition of Claim 244 wherein L is a glyceryl ester.

265. A kit comprising a container holding a metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

266. The kit of Claim 265 wherein each P_3 contains 2-10 amino acids.

267. The kit of Claim 265 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa₁ Xaa₂ His; or

Xaa₁ Xaa₂ His Xaa₃; and

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

268. The kit of Claim 267 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

269. The kit of Claim 267 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

270. The kit of Claim 267 wherein Xaa₃ is lysine.

271. The kit of Claim 267 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

272. The kit of Claim 271 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

273. The kit of Claim 272 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

274. The kit of Claim 273 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

275. The kit of Claim 267 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

276. The kit of Claim 275 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

277. The kit of Claim 267 wherein both P₃ peptides are P₁.

278. The kit of Claims 265 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₃ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

279. The kit of Claim 265 wherein P₃ comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P₃.

280. The kit of Claim 265 wherein L is neutral.

281. The kit of Claim 265 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

282. The kit of Claim 281 wherein L contains 2-8 carbon atoms.

283. The kit of Claim 265 wherein L is a cyclic alkane residue containing from 2-8 carbon atoms.

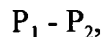
284. The kit of Claim 283 wherein L contains 3-5 carbon atoms.

285. The kit of Claim 265 wherein L is a nitrogen-containing heterocyclic alkane residue.

286. The kit of Claim 285 wherein L is a piperazide.

287. The kit of Claim 265 wherein L is a glyceryl ester.

288. A peptide having the formula:



wherein:

P_1 is:

Xaa_1 Xaa_2 His: or

Xaa_1 Xaa_2 His Xaa_3 ;

P_2 is $(Xaa_4)_n$;

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_2 is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa_3 is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa_4 is any amino acid;

n is 0-100; and

at least one amino acid of P_1 is a D-amino acid;

or a physiologically-acceptable salt thereof.

289. The peptide of Claim 288 wherein Xaa_1 is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

290. The peptide of Claim 288 wherein Xaa_2 is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

291. The peptide of Claim 288 wherein Xaa_3 is lysine.

292. The peptide of Claim 288 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

293. The peptide of Claim 292 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

294. The peptide of Claim 293 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

295. The peptide of Claim 294 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

296. The peptide of Claim 288 wherein n is 0-10.

297. The peptide of Claims 296 wherein n is 0-5.

298. The peptide of Claim 297 wherein n is 0.

299. The peptide of Claim 288 wherein P₂ comprises a metal-binding sequence.

300. The peptide of Claim 299 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His(Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₃ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

301. The peptide of Claim 300 wherein Xaa₅ is Orn or Lys.

302. The peptide of Claim 288 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids.

303 The peptide of Claim 302 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

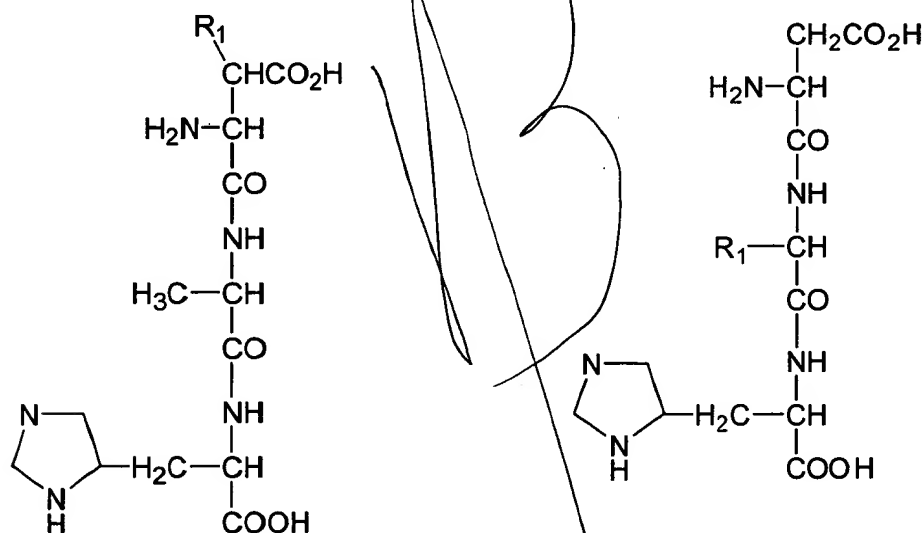
304. The peptide of Claim 288 wherein at least 50% of the amino acids of P₂ are D-amino acids.

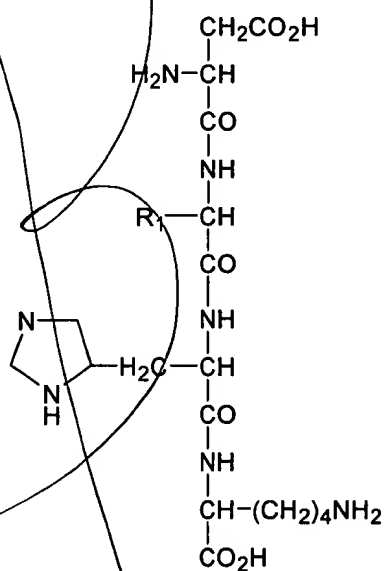
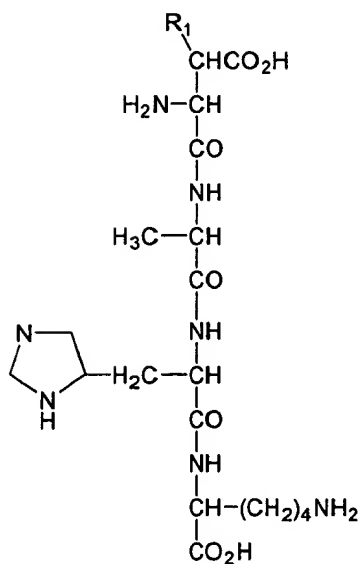
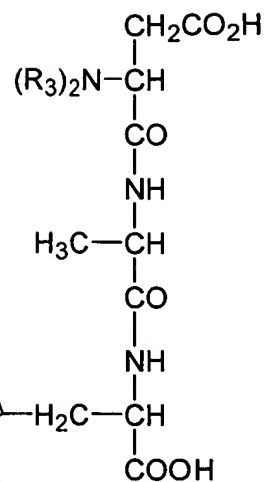
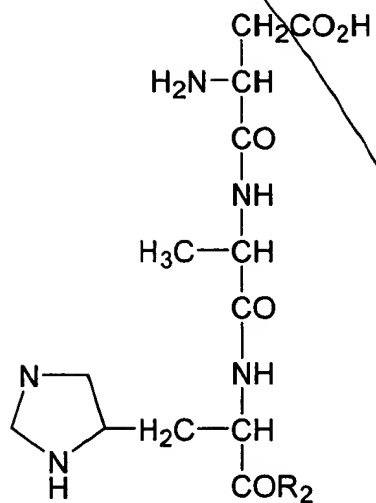
305. The peptide of Claim 302 wherein at least 50% of the amino acids of P₂ are D-amino acids.

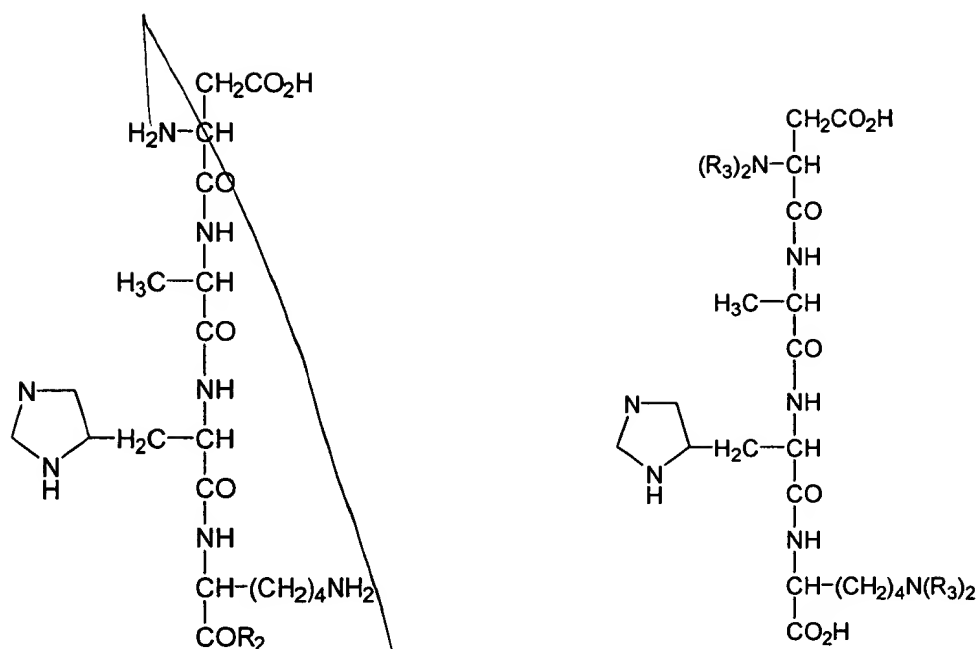
306. The peptide of Claim 303 wherein at least 50% of the amino acids of P_2 are D-amino acids.

a 307. The peptide of any one of Claims ~~288-306~~ wherein at least one amino acid of P_1 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

308. The peptide of Claim 307 wherein P_1 has one of the following formulas:







wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

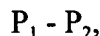
R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

309. The peptide of any one of Claims 288-306 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

310. The peptide of Claim 308 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes

without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions

311. A peptide having the formula:



wherein:

P_1 is:

Xaa₁ Xaa₂ His: or

Xaa₁ Xaa₂ His Xaa₃;

P_2 is (Xaa₄)_n;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

Xaa₄ is any amino acid;

n is 0-100; and

at least one amino acid of P_1 , P_2 or both is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.;

or a physiologically-acceptable salt thereof.

312. The peptide of Claim 311 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

313. The peptide of Claim 311 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

314. The peptide of Claim 311 wherein Xaa₃ is lysine.

315. The peptide of Claim 311 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

316. The peptide of Claim 315 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

317. The peptide of Claim 316 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

318. The peptide of Claim 317 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

319. The peptide of Claim 311 wherein n is 0-10.

320. The peptide of Claims 319 wherein n is 0-5.

321. The peptide of Claim 320 wherein n is 0.

322. The peptide of Claim 311 wherein P₂ comprises a metal-binding sequence.

323. The peptide of Claim 322 wherein P₂ comprises one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₂ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

wherein Xaa₅ is an amino acid having a free side-chain -NH₂ and m is 0-5.

324. The peptide of Claim 323 wherein Xaa₅ is Orn or Lys.

325. The peptide of Claim 311 wherein at least one of the amino acids of P₁ other than β -alanine is a D-amino acid.

326. The peptide of Claim 325 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids..

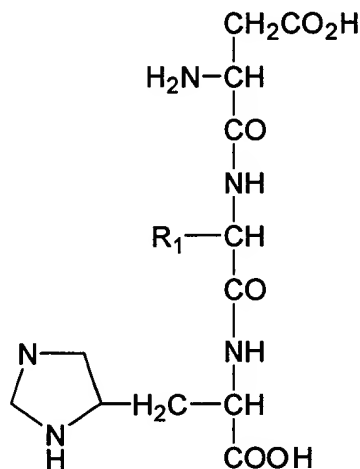
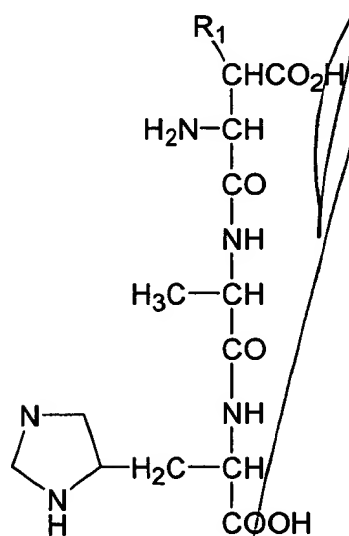
327. The peptide of Claim 326 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

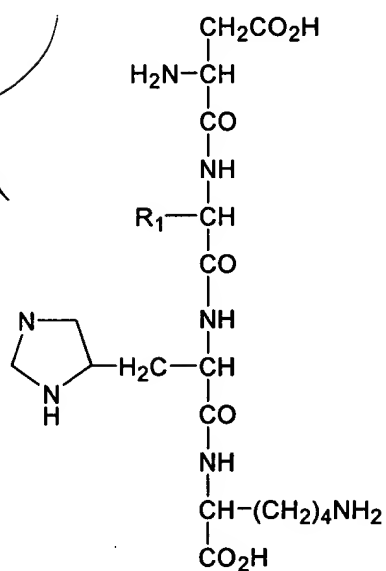
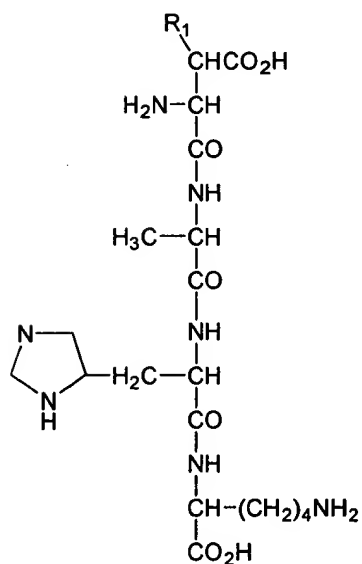
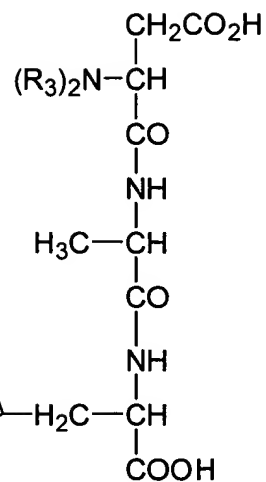
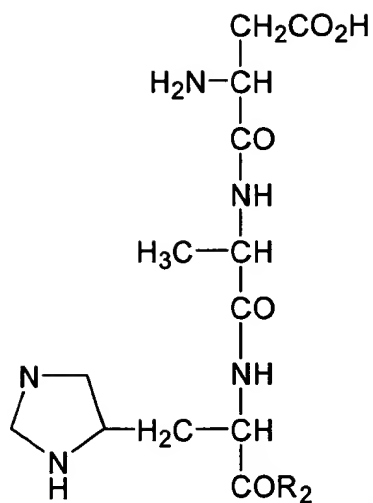
328. The peptide of Claim 325 wherein at least 50% of the amino acids of P_2 are D-amino acids.

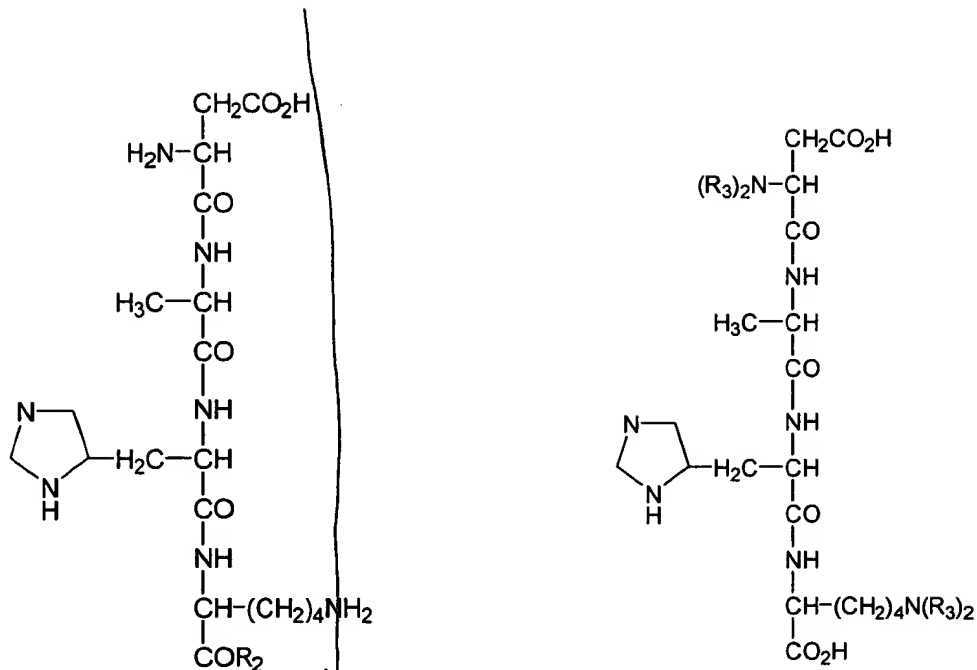
329. The peptide of Claim 326 wherein at least 50% of the amino acids of P_2 are D-amino acids.

330. The peptide of Claim 327 wherein at least 50% of the amino acids of P_2 are D-amino acids.

331. The peptide of any one of Claims 311-330 wherein P_1 has one of the following formulas:







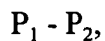
wherein:

R_1 is an alkyl, aryl, or heteroaryl;

R_2 is $-\text{NH}_2$, $-\text{NHR}_1$, $\text{N}(\text{R}_1)_2$, $-\text{OR}_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

332. A metal-binding peptide having the formula:



wherein:

P_1 is:

$\text{Xaa}_1 \text{Xaa}_2 \text{His}$; or

$\text{Xaa}_1 \text{Xaa}_2 \text{His Xaa}_3$;

P_2 is a peptide sequence which comprises the sequence of a metal binding site;

Xaa₁ is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan;

or a physiologically-acceptable salt thereof.

333. The peptide of Claim 332 wherein P₂ has one of the following sequences:

(Xaa₄)_m Xaa₃ His Xaa₂ Xaa₅,

(Xaa₄)_m His Xaa₂ Xaa₅,

(Xaa₄)_m Xaa₅ Xaa₃ His Xaa₃, or

(Xaa₄)_m Xaa₅ Xaa₂ His,

Xaa₄ is any amino acid;

Xaa₅ is an amino acid having a free side-chain -NH₂; and

m is 0-5.

334. The peptide of Claim 332 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

335. The peptide of Claim 332 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

336. The peptide of Claim 332 wherein Xaa₃ is lysine.

337. The peptide of Claim 332 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

338. The peptide of Claim 337 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

339. The peptide of Claim 338 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

340. The peptide of Claim 339 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

341. The peptide of Claim 333 wherein Xaa₅ is Orn or Lys.

342. The peptide of Claim 332 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

343. The peptide of Claim 342 wherein Xaa₁ is a D-amino acid, His is a D-amino acid, or both Xaa₁ and His are D-amino acids..

344. The peptide of Claim 343 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

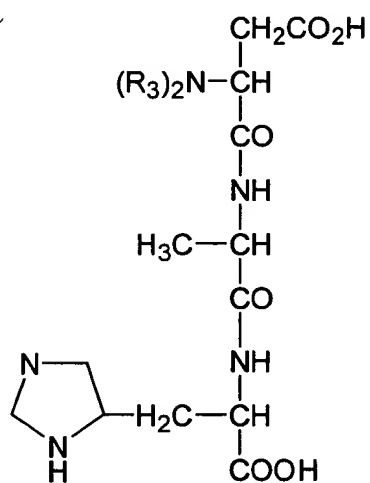
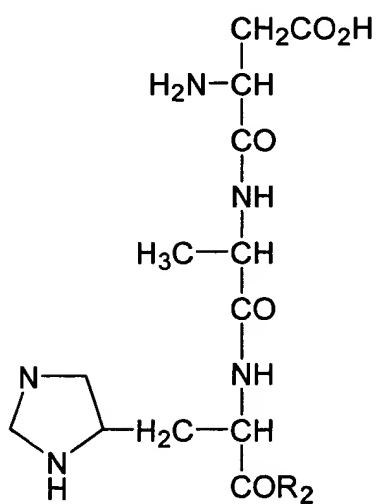
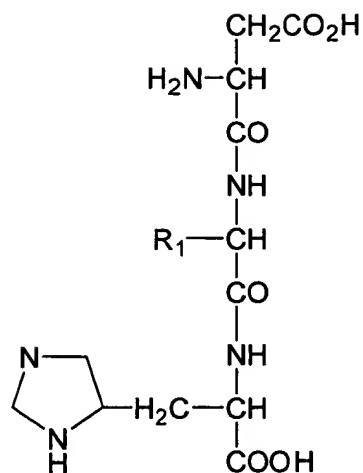
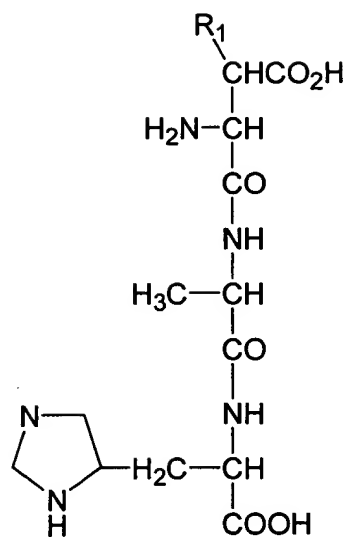
345. The peptide of Claim 342 wherein at least 50% of the amino acids of P₂ are D-amino acids.

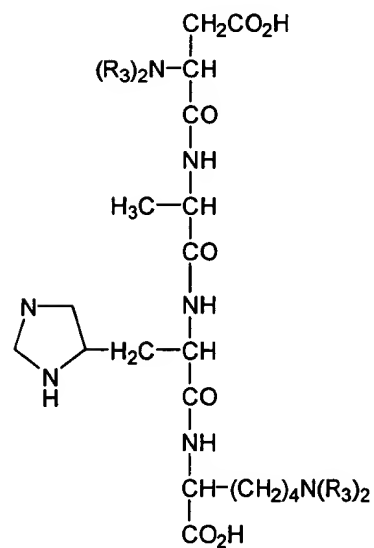
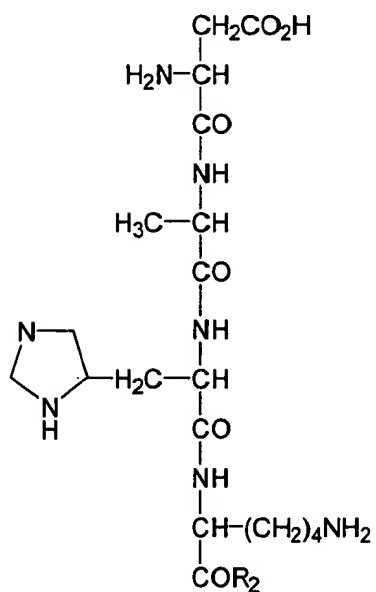
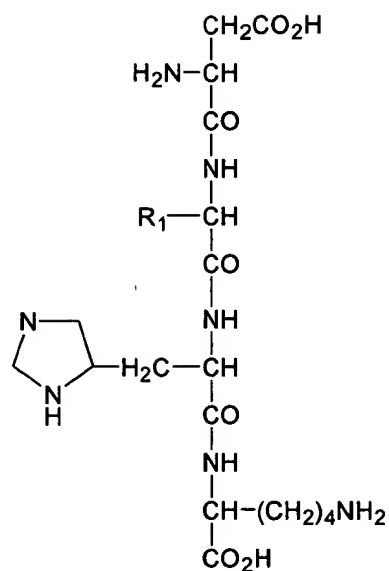
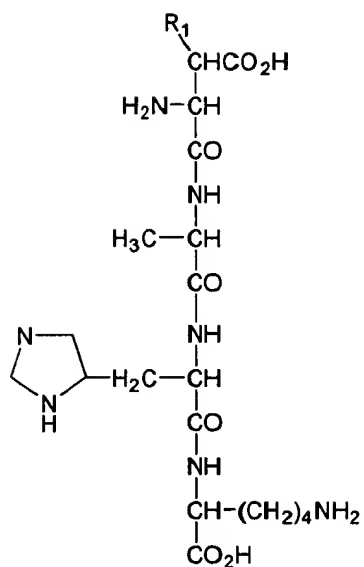
346. The peptide of Claim 343 wherein at least 50% of the amino acids of P₂ are D-amino acids.

347. The peptide of Claim 344 wherein at least 50% of the amino acids of P₂ are D-amino acids.

348. The peptide of any one of Claims 332-347 wherein at least one amino acid of P₁ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₁ to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P₁ to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

349. The peptide of Claim 348 wherein P₁ has one of the following formulas:





wherein:

R_1 is an alkyl, aryl, or heteroaryl;

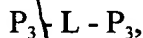
R_2 is $-NH_2$, $-NHR_1$, $N(R_1)_2$, $-OR_1$, or R_1 ; and

R_3 is H, a non-peptide, metal-binding functional group or the two R_3 groups together form a non-peptide, metal-binding functional group.

350. The peptide of any one of Claims 332-347 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions.

351. The peptide of Claim 348 wherein at least one amino acid of P_2 is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P_1 to bind metal ions, (b) a substituent that protects the peptide from proteolytic enzymes without altering the ability of P_1 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that increases the ability of the peptide to bind metal ions

352. A metal-binding peptide dimer of the formula:



wherein:

each P_3 may be the same or different and is a peptide which is capable of binding a metal ion; and

L is a chemical group which connects the two P_3 peptides through their C-terminal amino acids.

353. The peptide dimer of Claim 352 wherein each P_3 contains 2-10 amino acids.

354. The peptide dimer of Claim 352 wherein at least one P_3 is P_1 , wherein P_1 is:

Xaa_1 Xaa_2 His: or

Xaa_1 Xaa_2 His Xaa_3 and

Xaa_1 is glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine;

Xaa₂ is glycine, alanine, β -alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid, asparagine, glutamic acid, glutamine, lysine, hydroxylysine, histidine, arginine, ornithine, phenylalanine, tyrosine, tryptophan, cysteine, methionine, or α -hydroxymethylserine; and

Xaa₃ is glycine, alanine, valine, lysine, arginine, ornithine, aspartic acid, glutamic acid, asparagine, glutamine or tryptophan.

355. The peptide dimer of Claim 354 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine.

356. The peptide dimer of Claim 354 wherein Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine.

357. The peptide dimer of Claim 354 wherein Xaa₃ is lysine.

358. The peptide dimer of Claim 354 wherein Xaa₁ is aspartic acid, glutamic acid, arginine, or α -hydroxymethylserine, Xaa₂ is glycine, alanine, valine, leucine, isoleucine, threonine, serine, asparagine, methionine, histidine or α -hydroxymethylserine, and Xaa₃ is lysine.

359. The peptide dimer of Claim 358 wherein Xaa₁ is aspartic acid or glutamic acid and Xaa₂ is alanine, glycine, valine, threonine, serine, or α -hydroxymethylserine.

360. The peptide dimer of Claim 359 wherein Xaa₂ is alanine, threonine or α -hydroxymethylserine.

361. The peptide dimer of Claim 360 wherein Xaa₁ is aspartic acid and Xaa₂ is alanine.

362. The peptide dimer of Claim 354 wherein at least one amino acid of P₁ other than β -alanine is a D-amino acid.

363. The peptide dimer of Claim 354 wherein all of the amino acids of P₁ other than β -alanine are D-amino acids.

364. The peptide dimer of Claim 354 wherein both P₃ peptides are P₁.

365. The peptide dimer of Claims 352 wherein at least one amino acid of P₃ is substituted with (a) a substituent that increases the lipophilicity of the peptide without altering the ability of P₃ to bind metal ions, (b) a substituent that protects the peptide from proteolytic

enzymes without altering the ability of P_3 to bind metal ions, or (c) a substituent which is a non-peptide, metal-binding functional group that improves the ability of the peptide to bind metal ions.

366. The peptide dimer of Claim 352 wherein P_3 comprises an amino acid sequence which is substituted with a non-peptide, metal-binding functional group to provide the metal-binding capability of P_3 .

367. The peptide dimer of Claim 352 wherein L is neutral.

368. The peptide dimer of Claim 352 wherein L is a straight-chain or branched-chain alkane or alkene residue containing from 1-18 carbon atoms.

369. The peptide dimer of Claim 368 wherein L contains 2-8 carbon atoms.

370. The peptide dimer of Claim 352 wherein L is a cyclic alkane residue containing from 3-8 carbon atoms.

371. The peptide dimer of Claim 370 wherein L contains 3-5 carbon atoms.

372. The peptide dimer of Claim 352 wherein L is a nitrogen-containing heterocyclic alkane residue.

373. The peptide dimer of Claim 372 wherein L is a piperazide.

374. The peptide dimer of Claim 352 wherein L is a glyceryl ester.